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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/547,669	09/02/2005	Daniele Calistri	2503-1170	1643

466 7590 08/30/2010

YOUNG & THOMPSON
209 Madison Street
Suite 500
Alexandria, VA 22314

EXAMINER	
STAPLES, MARK	
ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
08/30/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DocketingDept@young-thompson.com

Office Action Summary	Application No.	Applicant(s)	
	10/547,669	CALISTRI ET AL.	
	Examiner	Art Unit	
	MARK STAPLES	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,9,10 and 12* is/are pending in the application.

4a) Of the above claim(s) *12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,9 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/12/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 9, and 10 consonant with original election of SEQ ID NOs: 9, 10, 13, 14, 15, and 15 are pending and at issue. Claim 12 remains withdrawn.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

2. The information disclosure statement filed on 07/12/2010 is considered.

Rejection Maintained

Claim Rejections Maintained - 35 USC § 103(a)

3. The rejection of claims 1, 9, and 10 under 35 U.S.C. 103(a) as being unpatentable over Shuber (2001), Kmiec et al. (W0 2001/73002), Albertsen et al. (US Patent No.: 6,114,124 issued 2001), and Buck et al. (1999) is maintained. Applicant's arugments are not persuasive. The rejection and response to arguments follow Table 1 below.

4. The following table is given for the discussion of prior art which follows.

Table 1

(re-provided from Office action mailed 03/28/2007)

100% Sequence Matches for SEQ ID NOs: 9, 10, 13, 14, 15, and 16

SEQ ID NO: 9

Search Result 20070214_162645_us-10-547-669a-9.rng.

```
Title:          US-10-547-669A-9
Perfect score:  20
Sequence:       1 aactaccatccagcaacaga 20
RESULT 3

AAF62231/c

ID   AAF62231 standard; DNA; 37 BP.

AC   AAF62231;

DT   21-MAY-2001  (first entry)

DE   Probe for human apc2 (adenomatous polyposis coli) gene.

KW   Human; detection; cancer; pre-cancer; foetal abnormality; apoptosis;

KW   colon cancer; probe; adenomatous polyposis coli; apc; ss.

OS   Homo sapiens.

PN   WO200118252-A2.

PD   15-MAR-2001.

PF   08-SEP-2000; 2000WO-US024639.

PR   08-SEP-1999;   99US-0152847P.

PR   07-DEC-1999;   99US-00455950.

PA   (EXAC-) EXACT LAB INC.

PI   Shuber AP;

DR   WPI; 2001-235215/24.

PT   Detecting a disease (e.g. cancer or pre-cancer), determining its status,

PT   or screening a patient for a disease, comprises determining the integrity

PT   of nucleic acids in a patient sample containing shed cells or cellular

PT   debris.
```

PS Example 3; Page 20; 44pp; English.

CC A method for determining the disease status of a patient or screening a
CC patient for disease, comprises determining the integrity of nucleic acids
CC in a sample containing cells which have been shed or cellular debris. The
CC method is useful for detecting a disease, determining the disease status
CC of a patient or screening a patient for a disease. The disease may be
CC cancer (e.g. colon cancer, lung cancer, oesophageal cancer, prostate
CC cancer, stomach cancer, pancreatic cancer, liver cancer or lymphoma) or
CC pre-cancer. The methods are also useful for assessing the integrity of
CC DNA in a biological sample or for assessing foetal abnormalities. The
CC methods are also useful as assays for apoptosis. The present sequence
CC represents a probe for human apc2 (adenomatous polyposis coli) DNA, which
CC is used in an example illustrating the use of the method for the
CC detection of colon cancer

SQ Sequence 37 BP; 5 A; 5 C; 12 G; 15 T; 0 U; 0 Other;

Query Match 100.0%; Score 20; DB 4; Length 37;

Best Local Similarity 100.0%; Pred. No. 9.3;

Matches 20; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

```
Qy          1 AACTACCATCCAGCAACAGA 20
              ||||||||||||||||||||
Db         35 AACTACCATCCAGCAACAGA 16
```

SEQ ID NO: 10

Search Result 20070214_162645_us-10-547-669a-10.rng.

Title: US-10-547-669A-10

Perfect score: 20

Sequence: 1 taatttggcataaggcatag 20

RESULT 2

ABA78740

ID ABA78740 standard; DNA; 121 BP.

AC ABA78740;

DT 24-JAN-2002 (first entry)

DE APC mutation correcting oligonucleotide SEQ ID NO: 1586.

KW Human; gene therapy; adenosine deaminase deficiency; p53; beta-globin;
KW retinoblastoma; BRCA1; BRCA2; CFTR; cystic fibrosis; cancer; Factor V;
KW cyclin-dependent kinase inhibitor 2A; CDKN2A; melanoma; APC; HBA1; HBA2;
KW adenomatous polyposis of the colon; Factor VII; Factor IX; thrombosis;
KW haemophilia; alpha thalassaemia; haemoglobin alpha locus 1; MLH1; APOE;
KW mismatch repair; MSH2; MSH6; hyperlipidaemia; apolipoprotein E; LDLR;
KW familial hypercholesterolaemia; UGT1; syndrome; APP; PSEN1; antisense;
KW UDP-glucuronosyltransferase; amyloid precursor protein; presenilin-1;
KW Alzheimer's disease; cytostatic; antisickling; antianaemic; haemostatic;
KW antilipemic; ss.

OS Homo sapiens.

PN WO200173002-A2.

PD 04-OCT-2001.

PF 27-MAR-2001; 2001WO-US009761.

PR 27-MAR-2000; 2000US-0192176P.

PR 27-MAR-2000; 2000US-0192179P.

PR 01-JUN-2000; 2000US-0208538P.

PR 30-OCT-2000; 2000US-0244989P.

PA (UYDE) UNIV DELAWARE.

PI Kmiec EB, Gamper HB, Rice MC;

DR WPI; 2001-639230/73.

XX

PT Oligonucleotide for targeted alterations of genetic sequences and for

PT treating cystic fibrosis, comprises at least one mismatch and chemical
PT modification.
PS Claim 7; Page 139; 294pp; English.
CC The present invention provides single-stranded oligonucleotides which can
CC be used for the targeted alteration of genomic sequences, where the
CC oligonucleotide has at least one mismatch compared with the genomic
CC sequence to be altered. In particular, these sequences are directed at
CC the following genes: adenosine deaminase, p53, beta-globin,
CC retinoblastoma, BRCA1, BRCA2, CFTR, cyclin-dependent kinase inhibitor 2A
CC (CDKN2A), APC, Factor V, Factor VIII, Factor IX, haemoglobin alpha locus
CC 1 (HBA1), haemoglobin alpha locus 2 (HBA2), MLH1, MSH2, MSH6,
CC apolipoprotein E (APOE), LDL receptor (LDLR), UDP-glucuronosyltransferase
CC (UGT1), amyloid precursor protein (APC), presenilin-1 (PSEN1) and
CC presenilin-2 (PSEN2). These can be used in the gene therapy of diseases
CC such as cancer, adenosine deaminase deficiency, cystic fibrosis,
CC haemophilia, hypercholesterolaemia, thalassaemia, sickle cell anaemia,
CC Alzheimer's disease, melanoma, adenomatous polyposis of the colon and
CC various syndromes. The present sequence is one of the gene correcting
CC oligonucleotides of the invention
SQ Sequence 121 BP; 30 A; 20 C; 25 G; 46 T; 0 U; 0 Other;

Query Match 100.0%; Score 20; DB 4; Length 121;
Best Local Similarity 100.0%; Pred. No. 3.1;
Matches 20; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

```
Qy          1 TAATTTGGCATAAGGCATAG 20
              ||||||||||||||||||||
Db          4 TAATTTGGCATAAGGCATAG 23
```

SEQ ID NO: 13

Search Result 20070214_162645_us-10-547-669a-13.rng.

Title: US-10-547-669A-13

Perfect score: 20

Sequence: 1 gatgtaatcagacgacacag 20

RESULT 2

ABA78836/c

ID ABA78836 standard; DNA; 121 BP.

AC ABA78836;

DT 24-JAN-2002 (first entry)

DE APC mutation correcting oligonucleotide SEQ ID NO: 1682.

KW Human; gene therapy; adenosine deaminase deficiency; p53; beta-globin;

KW retinoblastoma; BRCA1; BRCA2; CFTR; cystic fibrosis; cancer; Factor V;

KW cyclin-dependent kinase inhibitor 2A; CDKN2A; melanoma; APC; HBA1; HBA2;

KW adenomatous polyposis of the colon; Factor VII; Factor IX; thrombosis;

KW haemophilia; alpha thalassaemia; haemoglobin alpha locus 1; MLH1; APOE;

KW mismatch repair; MSH2; MSH6; hyperlipidaemia; apolipoprotein E; LDLR;

KW familial hypercholesterolaemia; UGT1; syndrome; APP; PSEN1; antisense;

KW UDP-glucuronosyltransferase; amyloid precursor protein; presenilin-1;

KW Alzheimer's disease; cytostatic; antisickling; antianaemic; haemostatic;

KW antilipemic; ss.

OS Homo sapiens.

PN WO200173002-A2.

PD 04-OCT-2001.

PF 27-MAR-2001; 2001WO-US009761.

PR 27-MAR-2000; 2000US-0192176P.

PR 27-MAR-2000; 2000US-0192179P.

PR 01-JUN-2000; 2000US-0208538P.

PR 30-OCT-2000; 2000US-0244989P.

PA (UYDE) UNIV DELAWARE.

PI Kmiec EB, Gamper HB, Rice MC;

DR WPI; 2001-639230/73.

PT Oligonucleotide for targeted alterations of genetic sequences and for
PT treating cystic fibrosis, comprises at least one mismatch and chemical
PT modification.

PS Claim 7; Page 144; 294pp; English.

CC The present invention provides single-stranded oligonucleotides which can
CC be used for the targeted alteration of genomic sequences, where the
CC oligonucleotide has at least one mismatch compared with the genomic
CC sequence to be altered. In particular, these sequences are directed at
CC the following genes: adenosine deaminase, p53, beta-globin,
CC retinoblastoma, BRCA1, BRCA2, CFTR, cyclin-dependent kinase inhibitor 2A
CC (CDKN2A), APC, Factor V, Factor VIII, Factor IX, haemoglobin alpha locus
CC 1 (HBA1), haemoglobin alpha locus 2 (HBA2), MLH1, MSH2, MSH6,
CC apolipoprotein E (APOE), LDL receptor (LDLR), UDP-glucuronosyltransferase
CC (UGT1), amyloid precursor protein (APC), presenilin-1 (PSEN1) and
CC presenilin-2 (PSEN2). These can be used in the gene therapy of diseases
CC such as cancer, adenosine deaminase deficiency, cystic fibrosis,
CC haemophilia, hypercholesterolaemia, thalassaemia, sickle cell anaemia,
CC Alzheimer's disease, melanoma, adenomatous polyposis of the colon and
CC various syndromes. The present sequence is one of the gene correcting
CC oligonucleotides of the invention

SQ Sequence 121 BP; 30 A; 24 C; 19 G; 48 T; 0 U; 0 Other;

Query Match 100.0%; Score 20; DB 4; Length 121;

Best Local Similarity 100.0%; Pred. No. 1.5;

```
Matches   20;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 GATGTAATCAGACGACACAG 20
              ||||||||||||||||||||
Db         78 GATGTAATCAGACGACACAG 59
```

SEQ ID NO: 14

```
Search Result 20070214_162645_us-10-547-669a-14.rng

Title:          US-10-547-669A-14
Perfect score:  20
Sequence:       1 ggcaatcgaacgactctcaa 20


RESULT 2

ABA78883/c

ID   ABA78883 standard; DNA; 121 BP.

AC   ABA78883;

DT   24-JAN-2002  (first entry)

DE   APC mutation correcting oligonucleotide SEQ ID NO: 1729.

KW   Human; gene therapy; adenosine deaminase deficiency; p53; beta-globin;

KW   retinoblastoma; BRCA1; BRCA2; CFTR; cystic fibrosis; cancer; Factor V;

KW   cyclin-dependent kinase inhibitor 2A; CDKN2A; melanoma; APC; HBA1; HBA2;

KW   adenomatous polyposis of the colon; Factor VII; Factor IX; thrombosis;

KW   haemophilia; alpha thalassaemia; haemoglobin alpha locus 1; MLH1; APOE;

KW   mismatch repair; MSH2; MSH6; hyperlipidaemia; apolipoprotein E; LDLR;

KW   familial hypercholesterolaemia; UGT1; syndrome; APP; PSEN1; antisense;

KW   UDP-glucuronosyltransferase; amyloid precursor protein; presenilin-1;

KW   Alzheimer's disease; cytostatic; antisickling; antianaemic; haemostatic;

KW   antilipemic; ss.

OS   Homo sapiens.

PN   WO200173002-A2.

PD   04-OCT-2001.
```

PF 27-MAR-2001; 2001WO-US009761.

PR 27-MAR-2000; 2000US-0192176P.

PR 27-MAR-2000; 2000US-0192179P.

PR 01-JUN-2000; 2000US-0208538P.

PR 30-OCT-2000; 2000US-0244989P.

PA (UYDE) UNIV DELAWARE.

PI Kmiec EB, Gamper HB, Rice MC;

DR WPI; 2001-639230/73.

PT Oligonucleotide for targeted alterations of genetic sequences and for
PT treating cystic fibrosis, comprises at least one mismatch and chemical
PT modification.

PS Claim 7; Page 146; 294pp; English.

CC The present invention provides single-stranded oligonucleotides which can
CC be used for the targeted alteration of genomic sequences, where the
CC oligonucleotide has at least one mismatch compared with the genomic
CC sequence to be altered. In particular, these sequences are directed at
CC the following genes: adenosine deaminase, p53, beta-globin,
CC retinoblastoma, BRCA1, BRCA2, CFTR, cyclin-dependent kinase inhibitor 2A
CC (CDKN2A), APC, Factor V, Factor VIII, Factor IX, haemoglobin alpha locu s
CC 1 (HBA1), haemoglobin alpha locus 2 (HBA2), MLH1, MSH2, MSH6,
CC apolipoprotein E (APOE), LDL receptor (LDLR), UDP-glucuronosyltransferase
CC (UGT1), amyloid precursor protein (APC), presenilin-1 (PSEN1) and
CC presenilin-2 (PSEN2). These can be used in the gene therapy of diseases
CC such as cancer, adenosine deaminase deficiency, cystic fibrosis,
CC haemophilia, hypercholesterolaemia, thalassaemia, sickle cell anaemia,
CC Alzheimer's disease, melanoma, adenomatous polyposis of the colon and
CC various syndromes. The present sequence is one of the gene correcting
CC oligonucleotides of the invention

SQ Sequence 121 BP; 28 A; 29 C; 28 G; 36 T; 0 U; 0 Other;

```
  Query Match             100.0%;  Score 20;  DB 4;  Length 121;

  Best Local Similarity   100.0%;  Pred. No. 2.1;

Matches   20;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 GGCAATCGAACGACTCTCAA 20
              ||||||||||||||||||||
Db         92 GGCAATCGAACGACTCTCAA 73
```

SEQ ID NO: 15

```
Search Result 20070214_162645_us-10-547-669a-15.rng.

Title:          US-10-547-669A-15
Perfect score:  20
Sequence:       1 cagtgatcttccagatagcc 20


RESULT 5

AAA93450

ID   AAA93450 standard; cDNA; 8229 BP.

AC   AAA93450;

DT   16-JAN-2001  (first entry)

DE   Human APC (DP2.5) cDNA (splice variant 2).

KW   APC gene; Adenomatous Polyposis Coli gene; human; chromosome 5q21;

KW   familial adenomatous polyposis; FAP locus; Gardner's syndrome; GS;

KW   sporadic tumour; adenoma; carcinoma; cancer; lung; breast; colon; rectum;

KW   bladder; liver; sarcoma; stomach; prostate; leukaemia; lymphoma;

KW   tumour suppressor; anti-APC antibody; detection; diagnosis; prognosis;

KW   genetic predisposition; drug screening; DP2.5; splice variant; ds.

OS   Homo sapiens.

PN   US6114124-A.

PD   05-SEP-2000.

PF   25-MAY-1995;   95US-00450582.
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PR 16-JAN-1991; 91GB-00000962.

PR 16-JAN-1991; 91GB-00000963.

PR 16-JAN-1991; 91GB-00000974.

PR 16-JAN-1991; 91GB-00000975.

PR 08-AUG-1991; 91US-00741940.

PR 12-AUG-1994; 94US-00289548.

PA (ICIL) IMPERIAL CHEM IND PLC.

PA (UYJO) UNIV JOHNS HOPKINS.

PA (UTAH) UNIV UTAH.

PA (CANC-) CANCER INST.

PI Carlson M, Groden J, Joslyn G, Kinzler K, Markham AF, Anand R;

PI Albertsen H, White RL, Thliveris A, Nakamura Y, Vogelstein B;

PI Hedge PJ;

DR WPI; 2000-565003/52.

DR P-PSDB; AAB23012.

PT Detecting Adenomatous Polypopsis Coli (APC) protein in a sample for

PT diagnosing cancers, involves contacting the sample with antibodies that

PT specifically bind to APC protein and detecting the complex formed.

PS Example 7; Fig 7A1-7W; 125pp; English.

CC The invention relates to a novel method for detecting Adenomatous

CC Polyposis Coli (APC) protein in a sample. The method involves contacting

CC the sample with antibodies which specifically binds to the 2843 amino

CC acid form of the human APC protein, or to a mutant APC protein, and

CC detecting an APC-antibody complex. Mutations in the APC gene play a role

CC in tumorigenesis, indicating that it is a tumour suppressor gene. It is

CC located on chromosome 5q21, which corresponds to the FAP (familial

CC adenomatous polyposis) locus. FAP is an autosomal dominant inherited

CC disease in which affected individuals develop hundreds to thousands of

CC adenomatous polyps in the colon and rectum, some of which progress to
CC malignancy. The FAP locus is often found to be deleted in sporadic (i.e.,
CC non-familial) adenomas and carcinomas, and chromosome 5q deletions have
CC also been observed in tumours of the lung, breast, colon, rectum,
CC bladder, liver, sarcomas, stomach, and prostate, and in leukaemias and
CC lymphomas. Although the FAP locus contains several other genes such as
CC FER, TB1, TB2, and MCC, it is thought that mutations in the APC gene play
CC a key role in the development of FAP and sporadic tumours. The method is
CC useful for detecting APC protein and its mutant forms in foetal tissue,
CC placental tissue, amniotic fluid, blood, serum or a tumour sample. The
CC method is useful for diagnosing or prognosing neoplastic tissue, for
CC detecting a genetic predisposition to cancer, for detecting germline and
CC somatic alteration of wild-type APC genes, and for testing therapeutic
CC agents for the ability to suppress tumours. The present sequence
CC represents cDNA encoding a 2742 amino acid splice variant of the human
CC APC protein

SQ Sequence 8229 BP; 2863 A; 1702 C; 1670 G; 1994 T; 0 U; 0 Other;

Query Match 100.0%; Score 20; DB 3; Length 8229;
Best Local Similarity 100.0%; Pred. No. 9.8;
Matches 20; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 CAGTGATCTTCCAGATAGCC 20
||||||||||||||||||||
Db 3957 CAGTGATCTTCCAGATAGCC 3976

SEQ ID NO: 16

Search Result 20070214_162645_us-10-547-669a-16.rng.

Title: US-10-547-669A-16

Perfect score: 20

Sequence: 1 aaatggctcatcgaggctca 20

RESULT 2

ABA78900

ID ABA78900 standard; DNA; 121 BP.

AC ABA78900;

DT 24-JAN-2002 (first entry)

DE APC mutation correcting oligonucleotide SEQ ID NO: 1746.

KW Human; gene therapy; adenosine deaminase deficiency; p53; beta-globin;

KW retinoblastoma; BRCA1; BRCA2; CFTR; cystic fibrosis; cancer; Factor V;

KW cyclin-dependent kinase inhibitor 2A; CDKN2A; melanoma; APC; HBA1; HBA2;

KW adenomatous polyposis of the colon; Factor VII; Factor IX; thrombosis;

KW haemophilia; alpha thalassaemia; haemoglobin alpha locus 1; MLH1; APOE;

KW mismatch repair; MSH2; MSH6; hyperlipidaemia; apolipoprotein E; LDLR;

KW familial hypercholesterolaemia; UGT1; syndrome; APP; PSEN1; antisense;

KW UDP-glucuronosyltransferase; amyloid precursor protein; presenilin-1;

KW Alzheimer's disease; cytostatic; antisickling; antianaemic; haemostatic;

KW antilipemic; ss.

OS Homo sapiens.

PN WO200173002-A2.

PD 04-OCT-2001.

PF 27-MAR-2001; 2001WO-US009761.

PR 27-MAR-2000; 2000US-0192176P.

PR 27-MAR-2000; 2000US-0192179P.

PR 01-JUN-2000; 2000US-0208538P.

PR 30-OCT-2000; 2000US-0244989P.

PA (UYDE) UNIV DELAWARE.

PI Kmiec EB, Gamper HB, Rice MC;

DR WPI; 2001-639230/73.

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PT treating cystic fibrosis, comprises at least one mismatch and chemical
PT modification.

PS Claim 7; Page 147; 294pp; English.

CC The present invention provides single-stranded oligonucleotides which can
CC be used for the targeted alteration of genomic sequences, where the
CC oligonucleotide has at least one mismatch compared with the genomic
CC sequence to be altered. In particular, these sequences are directed at
CC the following genes: adenosine deaminase, p53, beta-globin,
CC retinoblastoma, BRCA1, BRCA2, CFTR, cyclin-dependent kinase inhibitor 2A
CC (CDKN2A), APC, Factor V, Factor VIII, Factor IX, haemoglobin alpha locus
CC 1 (HBA1), haemoglobin alpha locus 2 (HBA2), MLH1, MSH2, MSH6,
CC apolipoprotein E (APOE), LDL receptor (LDLR), UDP-glucuronosyltransferase
CC (UGT1), amyloid precursor protein (APC), presenilin-1 (PSEN1) and
CC presenilin-2 (PSEN2). These can be used in the gene therapy of diseases
CC such as cancer, adenosine deaminase deficiency, cystic fibrosis,
CC haemophilia, hypercholesterolaemia, thalassaemia, sickle cell anaemia,
CC Alzheimer's disease, melanoma, adenomatous polyposis of the colon and
CC various syndromes. The present sequence is one of the gene correcting
CC oligonucleotides of the invention

SQ Sequence 121 BP; 38 A; 26 C; 24 G; 33 T; 0 U; 0 Other;

Query Match 100.0%; Score 20; DB 4; Length 121;
Best Local Similarity 100.0%; Pred. No. 1.9;
Matches 20; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

```
Qy          1 AAATGGCTCATCGAGGCTCA 20
              ||||||||||||||||||||
Db         24 AAATGGCTCATCGAGGCTCA 43
```

New Rejections Prompted by IDS Submission

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1, 9, and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber (2001, previously cited), Kmiec et al. (W0 2001/73002, previously cited),

Albertsen et al. (US Patent No.: 6,114,124 issued 2001, previously cited), and Buck et al. (1999, previously cited).

Regarding claims 1 and 9, Shuber teaches a method for determining the presence of colorectal tumors in a human subject (entire reference), which comprises:

a) extracting DNA from stool samples (see p. 18, 1st paragraph: "After homogenization, nucleic acid is preferably isolated from the stool sample. . . .The extracted nucleic acids are then precipitated with alcohol. . . . Total DNA is isolated using techniques known in the art");

b) PCR amplifying at least three different DNA fragments with a length of 100 base pairs or more, using deoxynucleotide triphosphates or primers labeled with detectable markers (see p. 4, 2nd paragraph, 6th sentence: "It is preferable that, in the case of DNA, the amplification reaction is a polymerase chain reaction (PCR) . . ." ; p. 9, 2nd paragraph : "Methods of the invention also comprise conducting a series of amplification reactions at a series of different genomic loci. . . . Preferably, from about 2 to about 7 amplification reactions on about 2 to about 7 loci are used. . . . In a preferred embodiment, the target fragment lengths are 200 bp, 400 bp, 800 bp, 1.3 Kb, 1.8 Kb, and 2.4 Kb" which are more than 100 base pairs and note that 200 and 400 are between 100 and 500 base pairs as recited in instant claim 5; and p. 8, 2nd paragraph, 3rd sentence: "Labels, such as fluorescent or radioactive labels, may be used" which also applies to instant claim 2);

c) quantifying the amplified fragments (amplicons);

d) calculating the total amount of different amplicons;

e) comparing the values obtained in (d) with a reference value (for steps c, d, and e see Figures 1 through 10, where quantitation is given as "Q#", which is calculated by interpolation, as recited in instant claim 9, from a standard curve consisting of known amounts of DNA, and compared to the "NEG CONTROL" as a reference value, and in Figures 1-7 is also compared to the "POSITIVE CONTROL" as another reference value). Shuber further teaches that a total amount of amplicons, that is amplifiable nucleic acid, is indicative of disease by teaching: "As shown in those figures [11A and 11B], patients with [colorectal] cancer or adenoma have an increased yield of amplifiable DNA." (see p. 22 lines 20 and 21).

Further regarding claim 1, Shuber teaches as noted above, including amplification of APC fragments and teaches a sequence comprising SEQ ID NO: 9 (see Table 1 of Office Action above).

Further regarding claim 1, Shuber teaches a method where the reference value is determined from healthy (normal) subjects/patients (See p. 3, 2nd paragraph, 5th sentence: "Thus, tumor cells are typically intact and routinely are shed into, for example, stool, sputum, urine, bile, pancreatic juice, and blood. Such shed cells and cellular debris contain higher integrity nucleic acids and other cellular components compared to those found in specimens obtained from a healthy patient"; and see p. 10, 2nd paragraph, 3rd sentence: "A baseline for comparison of the extent of nucleic acid amplification can be amounts of nucleic acids from known normal samples").

Further regarding claim 1, Shuber teaches a method wherein at least 8 different DNA fragments are amplified (12 loci for amplification are taught which is at least eight,

as given on p. 8, 1st paragraph, last sentence: "Preferred disease-associated loci include p53, apc, MSH-2, dcc, scr, c-myc, B-catnenin, mlh-1 , pms-I , pms-2, pol-delta, and bax").

Furthermore the optimization of amplification through selection of primer sequences, placement of primer seuqences, and other factors affecting results for cancer detection was known in the prior art as taught by Shuber:

> "Each of the methods described above are based upon the principle that an intact nucleic acid, or a segment of an intact nucleic acid, in a sample is diagnostic. Thus, variations on the methods described above are contemplated. Such variations include the **placement of primers**, the number of primers used, the target sequence, the **method for identifying sequences, and others**. For example, in the method depicted in Figure 13, and described above, it is not necessary that the numbers of forward and reverse primers be equal. A forward primer may, for example, be used to amplify fragments between two reverse primers. **Other variations in primer pair placement** are within the skill in the art, as are details of the amplification reactions to be conducted. Finally, as represented in Figures 12 and 13, capture probes may be used in methods of the invention in order to isolate a chosen target sequence" (emphasis by Examiner, see the 1st paragraph on p. 17).

Shuber does not teach other elected sequences of instant claim 1 comprising SEQ ID NOs: 10, 13, 14, 15, and 16.

Regarding claim 10, Shuber teaches spectrophotometric detection systems (see p. 8, 2nd paragraph, 3rd sentence: "The amounts of amplification product produced may be compared to standard amounts by any suitable or convenient means, including, but not limited to... machine-driven optical comparison, densitometry,.., and other known means").

Kmiec et al. teach sequences comprising SEQ ID NO: 10 and 16, and teaches sequences comprising the sequences in primer pairs SEQ ID NOs: 13 and 14 (see Table 1 above).

Kmiec et al. do not teach SEQ ID NOs: 9 and 15 or sequences comprising these.

Albertsen et al. teach a sequence comprising SEQ ID NO: 15 (see Table 1 of Office Action mailed on 03/28/2007).

Albertsen et al. do not teach SEQ ID NOs: 9, 10, 13, 14, or 16; or sequences comprising these.

Buck et al. do not teach SEQ ID NOs: 9, 10, 13, 14, 15, or 16; or sequences comprising these.

Claim 1 is rejected for SEQ ID NOs: 9, 10, 13, 14, 15, and 16, as described following. With regard to Claim 1, for primers designed for amplification of APC gene, Shuber, Kmeic et al. and Albertsen et al. expressly disclose the identical nucleic acid sequences presented in SEQ ID NOs: 9, 10, 13, 14, 15, and 16 of the instant invention. It is noted that the instant primer sites of SEQ ID NOs: SEQ ID NO: 9, 10, 13, 14, 15, and 16 are contained within the sequences disclosed by Shuber, Kmeic et al. and Albertsen et al.

The above described references do not specifically disclose the identical primer sequences of SEQ ID NO: 9, 10, 13, 14, 15, and 16 of the primers pairs, respectively, used in the claimed invention.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general

method of identifying a specific DNA does not make the specific DNA obvious.

Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers of the APC gene and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck et al (1999) expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of

extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Response to Arguments

8. Applicant argues that the results of Table 1 of the Declaration filed 01/22/2009 shows different results between the instantly claimed primers and new primers. Examiner agrees but this difference by itself does not demonstrate the claimed primers are novel or non obvious for determining the presence of colorectal tumors in view of the teachings of the prior art, as explained more below.

9. Applicant further argues that the claimed primers overall provide a higher sensitivity which reduces false negative results with false negative results having serious negative consequences for patient health. However, it is noted that the claimed primers and the new primers have respective sensitivities of 90% and 80% at the 10 ng cut-off. No error in measurement is provided with the data, so examining the data set as whole and noting the data are given in increments of 10% indicating the first digit is not significant, the available data suggest that a difference of 10% in sensitivity may well be within the error or measurement. Regardless, and at best due to absence of a range of variability in measurements, it is unknown whether the difference in sensitivity at the

10 ng cutoff is significant or not. In other words, at least at the 10 ng cut-off the sensitivity for determining the presence of colorectal cancer in methods using the claimed or new primers is similar and may well be within the error of measurement.

10. Applicant further argues that the teachings of Shuber and Buck are directed towards improvements in primers for amplification and not directed to improvements for colorectal cancer detection. However, both the claimed methods and those of Shuber use amplification to detect colorectal cancer, and so improvements to the amplification part are generally expected to improve the end result of colorectal cancer detection. Furthermore and to the contrary, Shuber also specifically teaches improving the placement of primers on known gene sequences for direct improvements of methods for detecting colorectal cancer. Even further and as given in detail above, Shuber teaches the claimed p53 and APC gene sequences were known, teaches these were amplified with primers to detect colorectal cancer, and teaches that variation in detection methods are contemplated including the primers placed to amplify fragments between two reverse primers and that: " Other variations in primer pair placement are well within the skill in the art, as are details of the amplification reactions to be conducted" (see 1st paragraph on p. 17). Thus, one of ordinary skill in the art at the time of the claimed invention would have been motivated by this teach to routinely optimize the placement of primers in the p53 and APC genes to improve detection of colorectal cancer. The placement of the claimed primers was thus routine optimization which would have been expected to yield improvements in cancer detection, in view of the prior teachings of Shuber and the other cited prior art.

Shuber also teaches detection using fluorescent labels and teaches quantitation of target DNA after amplification by comparison to standard amounts by any suitable, convenient, or known means (see 2nd paragraph on p. 8) and as given in detail above.

Applicant further points out that improvements in amplification could in fact be detrimental to the goal of detecting colorectal cancer; as by amplification of non specific sequences which would be expected to decrease detection of cancer by increasing false results. However, Shuber understood this and taught how to avoid false results, especially false negative results, by teaching: "The skilled artisan knows how to set thresholds depending on the patient (e.g., a lower threshold for patients with symptoms than patients presenting with no symptoms), the disease being diagnosed, and the desired level of sensitivity and specificity" (see last paragraph on p. 26). And as already discussed above the threshold/cut-off of 10 ng for the either the claimed or new primers would give comparable sensitivity.

11. The Information Disclosure Statement is considered. Applicant argues that the references submitted support the assertion that the claimed invention was not obvious in view of the prior art cited by Examiner. Applicant cites Callistri et al. (2004) as support that the claimed primers were novel. However, the claimed primers are not specifically taught by Callistri et al. who only references primers to p53 and APC genes in a general way (see 2nd column on p. 537). Thus Examiner cannot determine if the claimed primers are the same primers being used in Callistri et al. However it is noted that Callistri et al. use a similar method of multi-target detection as the claimed methods and convey that the multi-target detection was known (see 3rd paragraph on p. 539) in

the art prior to claimed invention, by citing Ahiquist et al. (2000, see reference no. 19 on p. 540).

Applicant further cites Schneeberger et al. (1995) as evidenced that the ethidium bromide used by Shuber is inferior to other reagents. However the instant claims which recite methods "comprising" do not exclude the use of ethidium bromide.

Applicant also cites the post filing art of Loktionov et al. (2007) as evidence that DNA extraction from stool was considered to be poor. Loktionov et al. do generally teach that cells directly collected from tissue are better than exfoliated cells in stool for determining colorectal cancer (see last paragraph on p. 2287) which questions the reliability of the claimed methods. The claimed methods are directed to stool samples and not to tissue samples. And Applicant has not presented evidence against this. Applicant has not presented evidence of the claimed primers detecting cancer in stool is comparable to or is better than detecting cancer in cells collected directly from tissue.

In summary, considering the totality of the teachings in the prior art and the evidence at hand; routine optimization for colorectal cancer detection in stool and thus the claimed methods, to the extent of the evidence provided, were obvious to one of ordinary skill in the art at the time of the claimed invention.

Conclusion

12. No claim is free of the prior art.

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Staples whose telephone number is (571) 272-9053. The examiner can normally be reached on Monday through Thursday, 9:00 a.m. to 7:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mark Staples/
Primary Examiner, Art Unit 1637
08/25/2010